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(54) Title: CONTROLLED RELEASE FORMULATION FOR ORAL ADMINISTRATION OF METFORMIN

(57) Abstract: A controlled release formulation for oral administration of metformin or a pharmaceutically acceptable salt thereof comprising metformin or a pharmaceutically acceptable salt thereof as an active ingredient; a combination of a polyethylene oxide and a natural gum as a carrier for controlled release; and a pharmaceutically acceptable additive.

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CONTROLLED RELEASE FORMULATION FOR ORAL ADMINISTRATION OF METFORMIN

Field of the Invention

The present invention relates to a controlled release formulation for oral administration of metformin or a pharmaceutically acceptable salt thereof.

Background of the Invention

Metformin is an oral medication designed to help control elevated blood sugar levels in non-insulin dependent diabetes mellitus (NIDDM) by activating glucose receptor in liver. It induces weight loss, reduces blood-triglyceride level and low-density lipoproteins (LDL), and increases high-density lipoproteins (HDL) in diabetic patient. Therefore, it may be used as a primary drug for NIDDM.

Metformin is currently marketed in the form of a hydrochloride as GLUCOPHAGE® (Bristol-myers Squibb Company) tablets and its daily dosage is determined individually on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended dose of 2,550 mg per day. The side effects of metformin are loss of appetite, abdominal distension, nausea and diarrhea while skin eruption or hives may break out rarely. These side effects may be avoided by reducing the minimum and/or maintenance dose, or by administrating a controlled release formulation.

Existing controlled release formulations of metformin are based on the use of polymers or release control by osmotic pressure. For example, WO 99/47128 discloses a two phase controlled release system based on polymers such as ethyl cellulose, sodium carboxy methyl cellulose and hydroxy propyl methyl cellulose with high water soluble medicament; WO 02/36100 discloses a method for controlling the release of medicament through the use of a perforated controlled release coating; and United States Patent No. 3,952,741 teaches an osmotic device comprising a semi permeable membrane.

However, the existing controlled release formulations have the problem

of high production costs and/or unsatisfactory release patterns.

Therefore, there has been a continual need to develop an economic controlled release formulation of metformin, which is capable of maintaining the effectiveness of the drug by uniform release over a prescribed period.

Summary of the Invention

Accordingly, it is an object of the present invention to provide a controlled release formulation of metformin, which can maintain uniform release of metformin for a long period of time and can be prepared easily.

In accordance with one aspect of the present invention, there is provided a controlled release formulation for oral administration of metformin or a pharmaceutically acceptable salt thereof comprising metformin or a pharmaceutically acceptable salt thereof as a pharmaceutically active ingredient; a combination of a polyethylene oxide and a natural gum as a carrier for controlled release; and a pharmaceutically acceptable additive.

Brief Description of Drawings

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the following accompanying drawings, which respectively show:

Fig. 1: *in vitro* release profiles of controlled release tablets prepared in Examples 1 to 4 of the present invention, and a comparative formulation (GLUCOPHAGE® XR controlled release tablet, Bristol-Myers Squibb Company);

Fig. 2: *in vitro* release profiles of the controlled release tablets prepared in Examples 5 to 8 of the present invention, and a comparative formulation (GLUCOPHAGE® XR controlled release tablet);

Fig. 3: *in vitro* release profiles of the controlled release tablets prepared

in Examples 9 to 12 of the present invention, and a comparative formulation (GLUCOPHAGE® XR controlled release tablet);

Fig. 4: *in vitro* release profiles of the controlled release tablets prepared in Example 2, and Comparative Examples 1 and 2;

Fig. 5: *in vitro* release profiles of the controlled release tablet prepared in Example 12 of the present invention as function of the rotation speed of the release port; and

Fig. 6: *in vitro* release profiles of a comparative formulation (GLUCOPHAGE® XR controlled release tablet) as function of the rotation speed of the release port.

Detailed Description of the Invention

The controlled release formulation for oral administration of metformin may be achieved by mixing a suitable metformin salt with a hydrophilic polymer to form solid particles. Employing a homologous and/or a heterologous hydrophilic polymer, the particles may be dispersed to formulate a compressed tablet or a packed capsule.

Each ingredient of said formulation is described in detail as follows:

(1) Pharmaceutically active ingredient

The active ingredient of the controlled release formulation of the present invention is metformin or its pharmaceutically acceptable salt, e.g., a hydrochloride, succinate or fumarate.

(2) Carrier for controlled release

The carrier for controlled release of the present invention is a combination of a polyethylene oxide and a natural gum. The polyethylene oxide may be chosen from the ones having average molecular weight between 100,000 and 7,000,000, or a mixture of two or more polyethylene oxides with different molecular weights may be also used.

The natural gum of the present invention refers to xanthan gum, locust

gum, guar gum, or a mixture thereof.

In accordance with the present invention, the weight ratio of the active ingredient : the carrier for controlled release may range from 1 : 0.01 to 1 : 1, and preferably, from 1 : 0.1 to 1 : 0.95.

(3) Pharmaceutically acceptable additive

The ingredients that can be supplemented to the formulation for controlled release include pharmaceutical additives acceptable for a solid formulation for oral administration such as neutralized diluent carriers, binders and lubricants.

The neutralized diluent carrier of the present invention can be lactose, dextrin, starch, microcrystallized cellulose, potassium phosphate monobasic, calcium carbonate, saccharide or silicon dioxide, and the like, which may contain conventional additives in the pharmaceutical field used in solid formulations for oral administration.

The binders of the present invention can be polyvinyl pyrrolidone or gelatin. Other conventional additives in the pharmaceutical field that are applied to solid formulation for oral administration can be also included.

The lubricants of the present invention can be a zinc or magnesium salt of stearic acid and the like, which may contain conventional additives in the pharmaceutical field used in solid formulations for oral administration.

In accordance with the present invention, the weight ratio of the active ingredient : the pharmaceutically acceptable additives may range from 1 : 0.001 to 1 : 0.3, preferably, from 1 : 0.01 to 1 : 0.1.

In order to have a more delicate control of active ingredient release, a selective release-controlling agent such as a wax or a polyvinyl acetate/polyvinyl pyrrolidone mixture, which helps the carrier for controlled release in manifesting its gel property *in vivo*, may be additionally used as an optional ingredient in the formulation of the present invention.

The weight ratio of the active ingredient : the said selective release controlling agent may preferably range from 1 : 0 to 1 : 0.9, whereas the ratio of total weight of the formulation : the agent can preferably range from 1 : 0 to 1 : 0.7.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Examples: Preparation of Metformin Controlled Release Tablet

Example 1

500g of metformin·HCl (Hwail Pharm. Co., Ltd), 80g of polyethylene oxide (Polyox® WSR Agglutinant, Molecular weight 5,000,000, Union Carbide) and 100 g of xanthan gum (Cpkelco) were each filtered through No. 30 mesh and mixed together. The mixture was placed in a high-speed mixer (SPG-2, Fujipaudal), and a binder solution made up of 20g of polyvinyl pyrrolidone (Kollidon® K-90, BASF) dissolved in distilled water was added to the mixer, followed by mixing at a speed of 100~1,000 rpm for 3min to obtain granules. The granules were dried and filtered through No. 30 mesh. Thereafter, 200g of a polyvinyl acetate/polyvinyl pyrrolidone mixture (Kollidon SR, BASF), 80g of wax (Compritol® 888ATO, Gattefosse) and 10g of silicon dioxide were added to the granules and mixed for 30 min. Finally, 10g of magnesium stearate powder was added to the mixture, mixed for 3 min, and compressed to obtain a tablet having the composition of Table 1.

Table 1

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	8
	Xanthan gum	10
	Polyvinyl pyrrolidone	2
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	8
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Examples 2 to 5

Tablets having the compositions listed in Tables 2 to 5 were prepared by repeating the procedure of Example 1 except for using Xanthan gum (Cpkelco) in the mixture part or using polyethylene oxides having different molecular weights. In addition, the binder, polyvinyl pyrrolidone was also excluded from the granule forming part in these examples.

Table 2: Composition of a tablet of Example 2

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	5
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	13
	Xanthan gum	10
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Table 3: Composition of a tablet of Example 3

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR N10, M.W 100,000)	5
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	13
	Xanthan gum	10
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Table 4: Composition of a tablet of Example 4

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR 1105, M.W 900,000)	5
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	13
	Xanthan gum	10
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Table 5: Composition of a tablet of Example 5

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	10
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	8
	Xanthan gum	10
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Example 6

A tablet having the composition shown in Table 6 was prepared by repeating the procedure of Example 1 except for not using the binder, polyvinyl pyrrolidone.

Table 6

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	10
	Xanthan gum	10
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	8
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Example 7

A tablet having the composition shown in Table 7 was prepared by repeating the procedure of Example 1 except for using isopropyl alcohol in place of distilled water during the granule formation step.

Table 7

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	8
	Xanthan gum	10
	Polyvinyl pyrrolidone	2
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Wax	8
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Examples 8 to 10

Tablets having the compositions shown in Tables 8 to 10 were prepared by repeating the procedure of Example 1 except for using a distilled water/isopropyl alcohol mixture (1:1 (v/v)) in place of distilled water during the granule formation step and not using the wax.

Table 8: Composition of a tablet of Example 8

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	8
	Xanthan gum	10
	Polyvinyl pyrrolidone	2
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	28
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Table 9: Composition of a tablet of Example 9

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	16
	Xanthan gum	10
	Polyvinyl pyrrolidone	2
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Table 10: Composition of a tablet of Example 10

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	8
	Xanthan gum	18
	Polyvinyl pyrrolidone	2
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Example 11

A tablet having the composition shown in Table 11 was prepared by repeating the procedure of Example 1 except for using a distilled water/isopropyl alcohol mixture (1:1 (v/v)) during the granule formation step as well as using xanthan gum (Cpkelco) and locust bean gum (Sigma) in the mixture part while not using the wax.

Table 11

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	10
	Polyvinyl pyrrolidone	2
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	20
	Xanthan gum	10
	Locust bean gum	6
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Example 12

A tablet having the composition listed in Table 12 was prepared by repeating the procedure of Example 11 except for not using the polyvinyl acetate/polyvinyl pyrrolidone mixture.

Table 12

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	50
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	10
	Polyvinyl pyrrolidone	2
Mixture part	Xanthan gum	21
	Locust bean gum	15
	Silicon dioxide	1
	Magnesium stearate	1
Total		100

Comparative Example 1

The tablet having the composition listed in Table 13 was prepared by repeating the procedure of Example 2 except for not using polyethylene oxide during granule formation.

Table 13

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	52.6
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	21.1
	Wax	13.7
	Xanthan gum	10.5
	Silicon dioxide	1.1
	Magnesium stearate	1
Total		100

Comparative example 2

A tablet having the composition listed in Table 14 was prepared by repeating the procedure of Example 2 except for not using xanthan gum.

Table 14

Ingredients		Content (wt%)
Granule forming part	Metformin· HCl	55.6
	Polyethylene oxide (Polyox® WSR, M.W 5,000,000)	5.6
Mixture part	Polyvinyl acetate/Polyvinyl pyrrolidone mixture	22.2
	Wax	14.4
	Silicon dioxide	1.1
	Magnesium stearate	1.1
Total		100

Test Example 1: *In vitro* Release-Test

The tablets prepared in Examples 1 to 12 and GLUCOPHAGE® XR controlled release tablet (Bristol-Myers Squibb Company) as a comparative formulation were subjected to *in vitro* release-test in accordance with the release-test method described in Korea pharmacopoeia (the paddle method) to compare the effects of natural gum and polyethylene oxide as carriers for controlled release on the release speed. The release patterns of metformin·HCl from each of the tablets were measured under the following conditions.

- Release-test system: Erweka DT 80
- Release solution: The disintegrating-test 2nd method described in Korea pharmacopoeia (artificial gastric fluid)
- Temperature of release solution: 37 ± 0.5 ℃
- Amount of release solution: 900 mL
- Rotation speed: 50 rpm

- Sample collection time: Aliquots of the release solution were collected at 1, 2, 3, 4, 6, 8, and 10 hr, filtered through a 0.45 μm membrane, and used as test samples. After sampling the release solution, the release-test system was refilled with an equal amount of fresh release solution.
- Analyzing method: Absorbances of the samples and a standard solution were measured at 233nm employing distilled water as a reference to calculate corresponding release ratios.
- Calculation of released amount: Cumulative release amount

As can be seen from Figs. 1 to 3, the release rate becomes slow as the amount of polyethylene oxide or the natural gum increases. Especially, the tablet of Example 14 releases the drug continuously in a release pattern similar to that of the comparative formulation.

Test Example 2: *In vitro* Release-Test

In vitro release-tests were conducted by repeating the method of Test Example 1, except for using the tablets prepared in Example 2, and Comparative Examples 1 and 2.

As can be seen from Fig. 4, tablets of Comparative Examples 1 and 2, which contain natural gum or polyethylene oxide alone as a carrier for controlled release show burst drug releases at the initial stage.

Test Example 3: *In vitro* Release-Test

In vitro release-tests were conducted for the tablet prepared in Example 12 and the comparative formulation by repeating the method of Test Example 1, except for changing the rotation speed to 100 rpm and 150 rpm.

As can be seen from Figs. 5 and 6, the tablet of Example 12 displays a steady release pattern equal to that of the comparative formulation, without initial burst release of the drug even at a high rotation speed.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made and also fall within the scope of the invention as defined by the claims that follow.

What is claimed is:

1. A controlled release formulation for oral administration of metformin or a pharmaceutically acceptable salt thereof comprising metformin or a pharmaceutically acceptable salt thereof as an active ingredient; a combination of a polyethylene oxide and a natural gum as a carrier for controlled release; and a pharmaceutically acceptable additive.

2. The controlled release formulation of claim 1, wherein the pharmaceutically acceptable salt of metformin is metformin hydrochloride, metformin succinate or metformin fumarate.

3. The controlled release formulation of claim 1, wherein the polyethylene oxide has an average molecular weight in the range of 100,000 to 7,000,000.

4. The controlled release formulation of claim 1, wherein the natural gum is selected from the group consisting of xanthan gum, locust bean gum, guar gum and a mixture thereof.

5. The controlled release formulation of claim 1, wherein the weight ratio of metformin or a pharmaceutically acceptable salt thereof : carrier ranges from 1 : 0.01 to 1 : 1.

Fig. 1

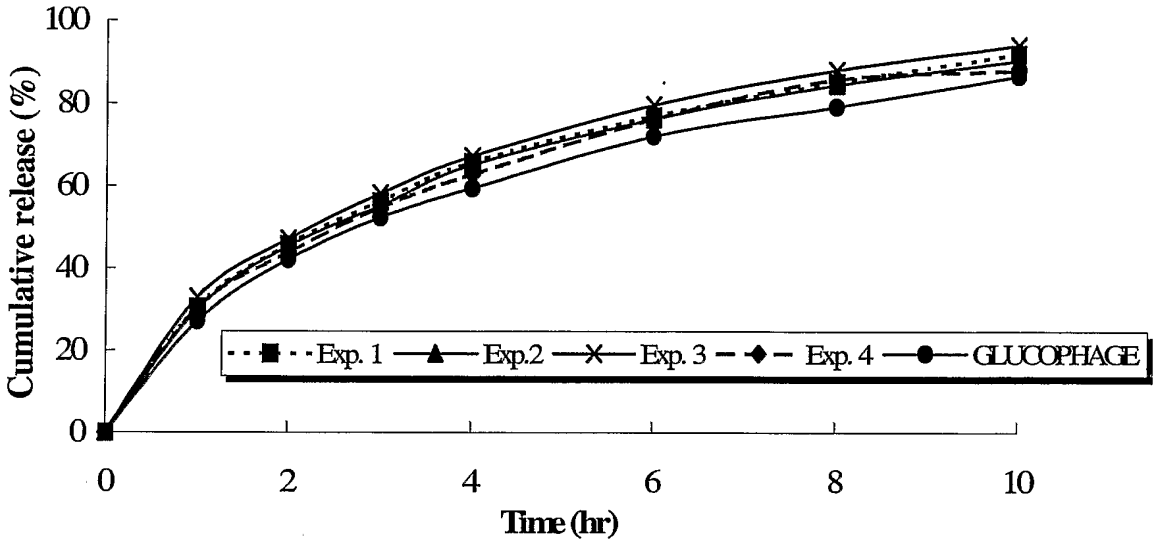
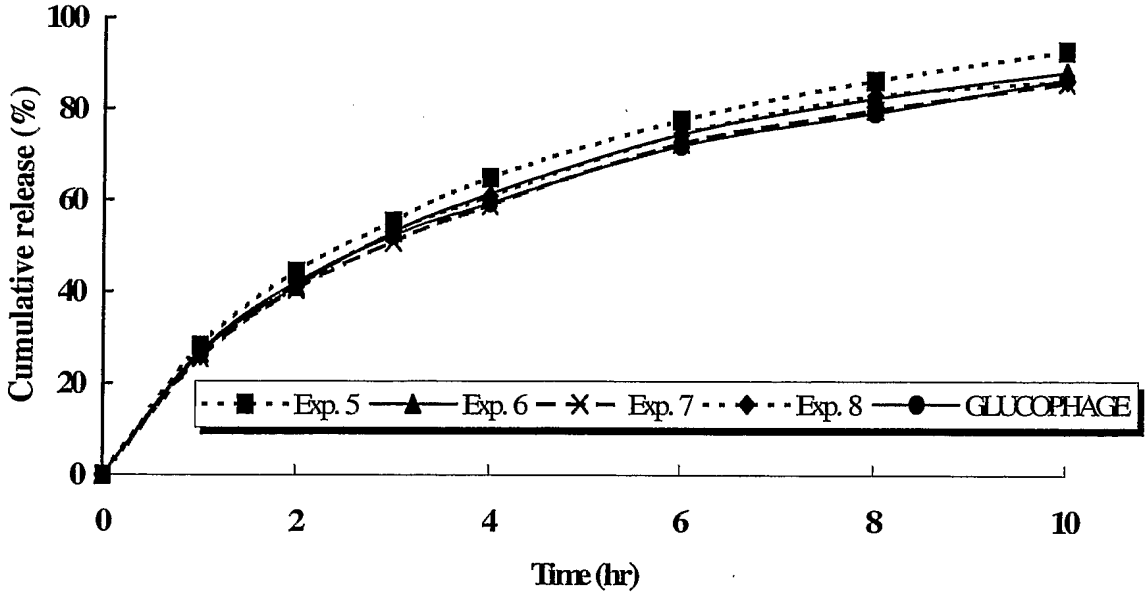

100
80
60
40
20
0
Cumulative release (%)
0
2
4
6
8
10
Time (hr)
Exp. 1
Exp.2
Exp. 3
Exp. 4
GLUCOPHAGE

Fig. 2


100
80
60
40
20
0
Cumulative release (%)
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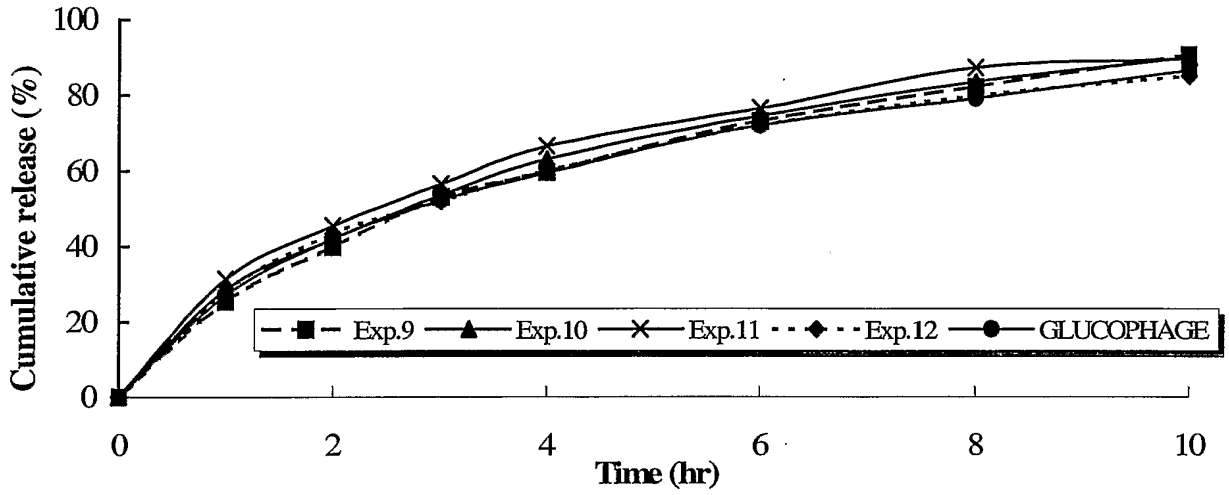
2
4
6
8
10
Time (hr)
Exp. 5
Exp. 6
Exp. 7
Exp. 8
GLUCOPHAGE

Fig. 3


Cumulative release (%)
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80
60
40
20
0
0
2
4
6
8
10
Time (hr)
Exp.9
Exp.10
Exp.11
Exp.12
GLUCOPHAGE

Fig. 4

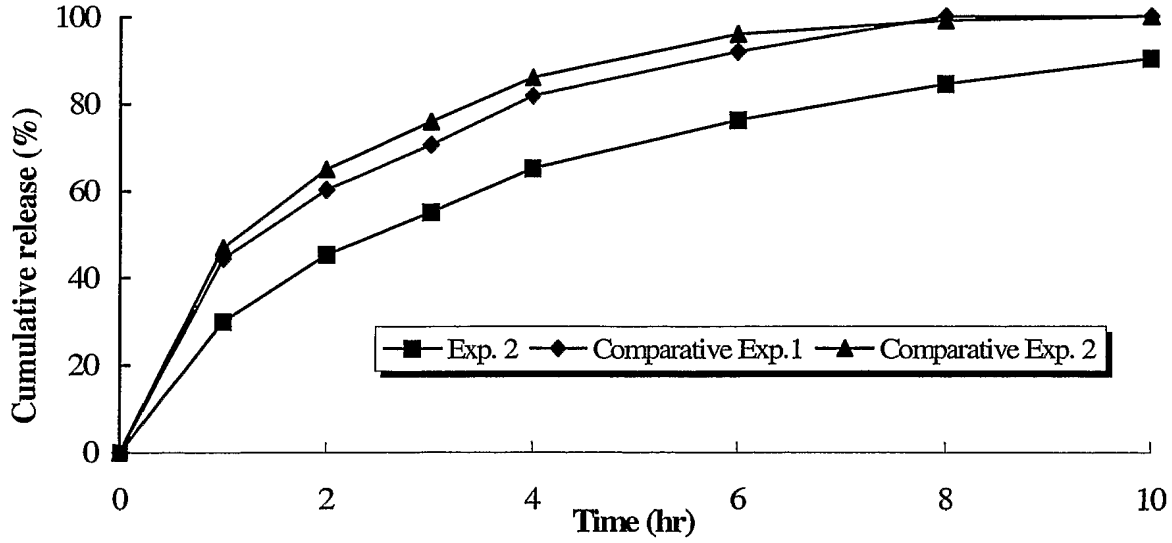

Cumulative release (%)
100
80
60
40
20
0
0
2
4
6
8
10
Time (hr)
Exp. 2
Comparative Exp.1
Comparative Exp. 2

Fig. 5

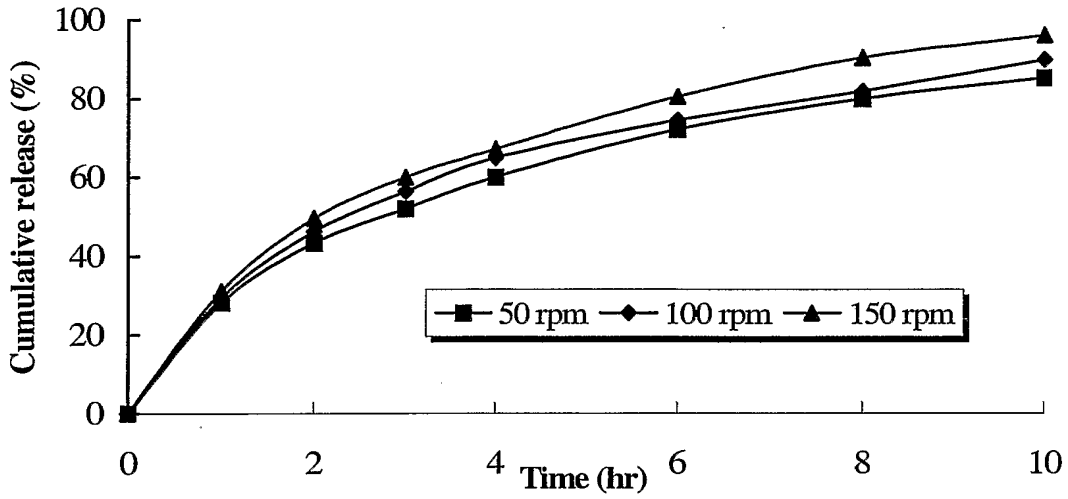
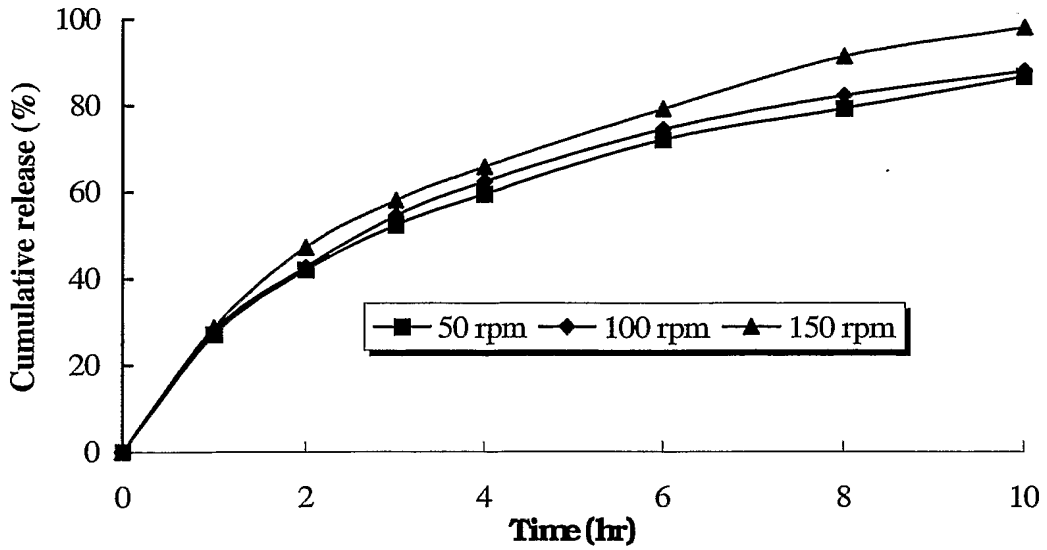

Cumulative release (%)
100
80
60
40
20
0
0
2
4
6
8
10
Time (hr)
50 rpm
100 rpm
150 rpm

Fig. 6


Cumulative release (%)
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80
60
40
20
0
0
2
4
6
8
10
Time (hr)
50 rpm
100 rpm
150 rpm

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/000936

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC:A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), BIOTECHNO(STN), SCISEARCH(STN), PROMT(STN), PASCAL(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,340,475 B2 (DEPOMED, INC.,) 22 JANUARY 2002 see the whole document, specially claim 3, 8, example 7	1-5
A	US 5,955,106 A (MOECKEL, JORN et al) 21 SEPTEMBER 1999 see the abstract and colum 3, line 25	1-5
A	US 6,517,866 B1 (PFIZER INC.,) 11 FEBRUARY 2003 see the column 37, line 39	1-5
A	Lalor BC et al, "Placebo-controlled trial of the effects of sugar gum and metformin on fasting blood glucose and serum lipids in obese, type 2 diabetic patients", University of Manchester Department of medicine, Diabetic Medicine, 1990, 3-4, Vol.7, No.3, pp.242-245	1-5
P, A	US 2004/0109891 A1 (PENWEST PHARMACEUTICALS COMPANY) 10 JUNE 2004 see the whole document	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 JULY 2005 (25.07.2005)	**27 JULY 2005 (27.07.2005)**

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CHANG, Jin Ah
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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/KR2005/000936

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